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Workshop on 'Nutritional models of the developmental origins of adult health and disease'

Session on 'Obesity'
Adipose tissue development, nutrition in early life and its impact on later obesity

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It is now apparent that one key factor determining the current obesity epidemic within the developed world is the extent to which adipose tissue growth and function can be reset in early life. Adipose tissue can be either brown or white, with brown fat being characterised as possessing a unique uncoupling protein (uncoupling protein 1) that enables the rapid generation of heat by non-shivering thermogenesis. In large mammals this function is recruited at approximately the time of birth, after which brown fat is lost, not normally reappearing again throughout the life cycle. The origin and developmental regulation of brown fat in large mammals is therefore very different from that of small mammals in which brown fat is retained throughout the life cycle and may have the same origin as muscle cells. In contrast, white adipose tissue increases in mass after birth, paralleled by a rise in glucocorticoid action and macrophage accumulation. This process can be reset by changes in the maternal nutritional environment, with the magnitude of response being further determined by the timing at which such a challenge is imposed. Importantly, the long-term response within white adipocytes can occur in the absence of any change in total fat mass. The present review therefore emphasises the need to further understand the developmental regulation of the function of fat through the life cycle in order to optimise appropriate and sustainable intervention strategies necessary not only to prevent obesity in the first place but also to reverse excess fat mass in obese individuals.

Pregnancy: Growth: Metabolism: Uncoupling proteins

Obesity is of immense importance, affecting almost all organ systems, and is a risk factor for hypertension, type 2 diabetes, cardiovascular mortality and renal disease. Ultimately, obesity is associated with an increased relative risk of mortality[1]. Whilst not all obese adults were overweight children, being overweight in childhood is a good predictor of excess fat mass as an adult[2]. Indeed, recent data have demonstrated a 16-fold increase in the prevalence of the metabolic syndrome in overweight adolescents compared with their normal-weight peers[3]. Furthermore, the adverse effects of early obesity appear to be exacerbated in those individuals previously exposed to a suboptimal nutritional environment *in utero*[4]. The understanding of the impact of early-life events on later susceptibility to obesity needs to include the pronounced changes in adipocyte lineage that commence *in utero* at critical stages of development. This information needs to be combined with a full appreciation of the substantial differences between the species used in animal investigations of obesity, to inform knowledge not only of fat distribution but also of how the interaction between diet and energy status can vary.

Adipocyte regulation in early life

There are at least two key factors in early life that are critical in determining adipose tissue function in the

Abbreviations: PRDM, PR-domain-containing; TLR4, toll-like receptor 4; UCP, uncoupling protein.

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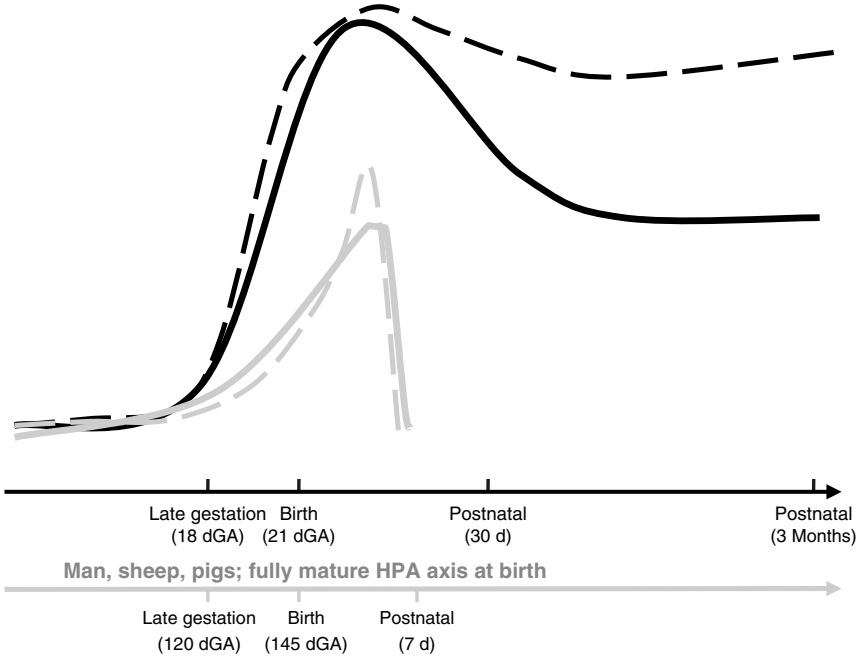

Fig. 1. Comparison of the ontogeny of uncoupling protein (UCP) 1 between small (—, – –) and large mammals (——, - - -). —, ——, UCP1 protein; – –, - - -, UCP1 mRNA; HPA, hypothalamic–pituitary–adrenal; dGA, d of gestation.

newborn: the amount of fat present and its ability to generate heat through the brown adipose tissue-specific uncoupling protein (UCP; UCP1)[5,6]. There are considerable differences in UCP1 both within different large-mammal species[7] and between small and large mammals[8]. For example, brown fat is not present in the newborn pig, which is dependent on shivering thermogenesis in order to maintain body temperature after birth[9]. In newborn sheep, which are primarily dependent on non-shivering thermogenesis in order to prevent newborn hypothermia, brown fat is rapidly recruited after birth[10]. In contrast, both mice and rats are precocial newborns and depend on huddling with their littermates within a nest in order to maintain body temperature[11]. Maturation of non-shivering thermogenesis at this time is therefore coincident with maturation of the hypothalamic–pituitary axis[12], a process that occurs over the final third of gestation in large mammals, including man, as compared with the lactational period in rodents[13]. Ultimately, these substantial differences in maturity at birth reflect the very different environments inhabited by each of the species, in conjunction with the profound differences in brain maturation that appear to have an over-riding influence on adipose tissue development[5].

The ontogeny of brown fat development

The most prominent example of differences in fat function and distribution resides within the ontogeny and location of brown fat between large and small mammals; primarily reflecting the very different methods of adapting to the extrauterine environment. In mice, for example, there is a precipitous rise in gene expression for UCP1 in late gestation (between 18 d and 19 d) that continues until $\geqslant$8 d after birth[14]. The abundance of UCP1 mRNA then declines by 1 month of age but is still retained throughout the life cycle (Fig. 1). This pattern contrasts with both human subjects and sheep in which UCP1 gradually increases in abundance through late gestation[15] to peak at birth[10] before declining over the first month to undetectable levels in sheep[16], a process that takes approximately 9 months after birth in human subjects[17]. These substantial differences between species must be given full consideration when considering the translational relevance of findings from small mammals to human subjects. Currently, for large mammals such as man and sheep there is no evidence that brown fat can be reactivated as, although there is some indirect evidence that brown fat is present in adult patients with cancer[18], its location is completely different from that seen in the newborn[17]. After the peak period of brown adipose tissue activation after birth not only is the UCP1 gene rapidly lost but this deficit is potentially accompanied by the *in vivo*, but not *in vitro*, loss of the key transcription factors PPARα and PPAR coactivator 1α[19] from ovine brown adipose tissue. At the same time, there is loss of glucose-regulated protein 78, an endoplasmic reticulum chaperone crucial for protein synthesis, that may further reflect the changes in protein content of adipocyte depots as they become primarily white in character[20]. Accompanying the loss of brown fat there is a substantial rise in the amount of white fat and white adipose tissue depots represent the fastest-growing organ[16].

Different origins of brown and white adipocytes

Recent studies have highlighted the importance of early-life events in determining aspects of adipocyte function

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and distribution. It has been shown that not only are white adipocyte progenitor cells committed to the adipose lineage during the late fetal–early postnatal period but there is also a marked expansion of this cellular pool as a result of proliferation during postnatal life[21]. It must be noted that in species adopted for the latter study (i.e. mice), this is the time at which changes in fat distribution are greatest[14]. In view of the strong possibility that the origin and fate of brown fat is very different between small and large mammals, it is important to reconsider the recent proposal that brown adipocytes have the same lineage as skeletal myoblasts, a process that may be regulated by bone morphogenetic protein 7 acting through PR-domain-containing (PRDM) 16[22,23]. The possibility of a common mechanism relating brown adipocyte and muscle development, and that it differs substantially from white adipocytes, is in accord with similarities between brown adipocytes and skeletal muscle and the distinct differences in myogenic gene expression found between brown and white cells[24]. Additionally, it has been suggested that functional brown fat may be present within muscle and other fat depots in some strains of mice[25] and the thymus in rats[26]. It is most unlikely that such depots have major biological importance[27] in overall energy balance as UCP1 protein is barely detectable[25]. This finding is not surprising, given that mRNA abundance for UCP1 in both skeletal muscle and fat sampled from the subcutaneous and epididymal regions is $<1\%$ of that found in native brown fat (located within the intrascapular region) even when maximally stimulated by a β_3-adrenergic agonist[25].

The UCP1 gene has also been identified in fetal, but not adult, human muscle-cell cultures[28]. Consequently, *UCP1* gene expression *in vitro* in fetal muscle CD34+ cells exhibits a much greater capacity to respond to the PPARγ agonist rosiglitazone than skeletal muscle cells isolated from adult human subjects[28]. However, the pronounced increase in UCP1 mRNA transcription seen in fetal, as compared with adult, muscle that has been allowed to differentiate *in vitro* (i.e. fetal 5·5-fold *v*. adult 0·5-fold) may simply reflect an exaggerated adaptation as a result of an inability to translate the greater abundance of UCP1 mRNA to protein. Indirect support for this proposal comes from the observation that maximal stimulation of PRDM-16-expressing myotubes still results in substantially lower protein expression of UCP1 compared with native brown adipocytes, whereas PRDM-16 is only present at very low levels in native brown fat[22]. Thus, it is likely that although PRDM-16 has a role in adipocyte cell lineage, this action only occurs very early in development. Consequently, in adults overexpression of PRDM-16 for 4 weeks, although promoting energy expenditure, has a much smaller effect on UCP1 gene expression[23]. One likely mediator of PRDM-16 action is through the sympathetic nervous system[29], which could also explain the 0·4°C rise in body temperature of these animals following transfection with PRDM-16[23]. Ultimately, it could be predicted that it is the increased physical activity and therefore heat production in lean mice[25] that acts to prevent excess fat accumulation. This process appears to act in combination with the persistently greater recruitment of non-exercise-activity thermogenesis, which is closely associated with a lower fat mass in adult human subjects[30].

Early determinants of fat cell number and fat growth

Studies in human subjects have demonstrated that adipocyte number is a major determinant of fat mass in adulthood, with the number of fat cells being set during childhood and adolescence and remaining largely unchanged through adulthood in both lean or obese individuals[31]. Importantly, the developmental up-regulation of adipocyte number with obesity appears to increase during infancy. Consequently, this process occurs 4 years earlier in obese (2·1 years) children compared with those that remain lean (5·7 years)[31]. The extent to which such a process maybe be reset by the early nutritional environment is unknown, but in species with a long gestation fat cells first appear at about mid gestation[32,33] before total fat mass increases up to term, as the fetus lays down sufficient energy reserves to enable it to meet the cold challenge of the extrauterine environment[15]. Importantly, the net effect is to promote the abundance of brown fat in the offspring[34,35] under thermal or nutritional environments that may act to enhance fetal development. In addition, term infants are born with substantial amounts of subcutaneous fat[36] that increase during lactation, before being mobilised during infancy with its increased energy expenditure in motor development. The postnatal period therefore encompasses a period in which there is a dramatic increase in total fat mass but modulation of fat depot location within the body[16].

Postnatal development of white adipose tissue

The loss of brown fat after birth, and subsequent replacement in fat mass depots by white adipocytes that have the potential for nearly 'unlimited' growth[16], is determined in part by changes in glucocorticoids[37]. Between 1 week and 6 months after birth, as fat mass increases in a linear fashion in animals raised in natural 'free-living' environments, there is an accompanying rise in glucocorticoid action within the adipocyte[37]. At the same time, the abundance of UCP2 peaks at approximately 30 d of age[37], coincident with the loss of UCP1[38]. As the switch from brown to white adipose tissue involves the proliferation and differentiation of preadipocytes and cell loss by apoptosis[39], UCP2 may be involved in the regulation of this transition[37].

Ultimately, with increasing fat mass and accompanying inflammation adipose tissue becomes insulin resistant and, if exposure to an obesogenic environment occurs, the metabolic syndrome may result[40]. As this process is a developmental one (see Fig. 2), it is essential that the normal changes within the adipocyte with increased age and fat mass are understood, as only then can appropriate intervention strategies be introduced to avoid the adverse metabolic consequences. Macrophage infiltration of adipose tissue contributes to the inflammatory state observed with obesity[41]. The mechanisms that drive this infiltration and alter insulin signalling remain unknown, although

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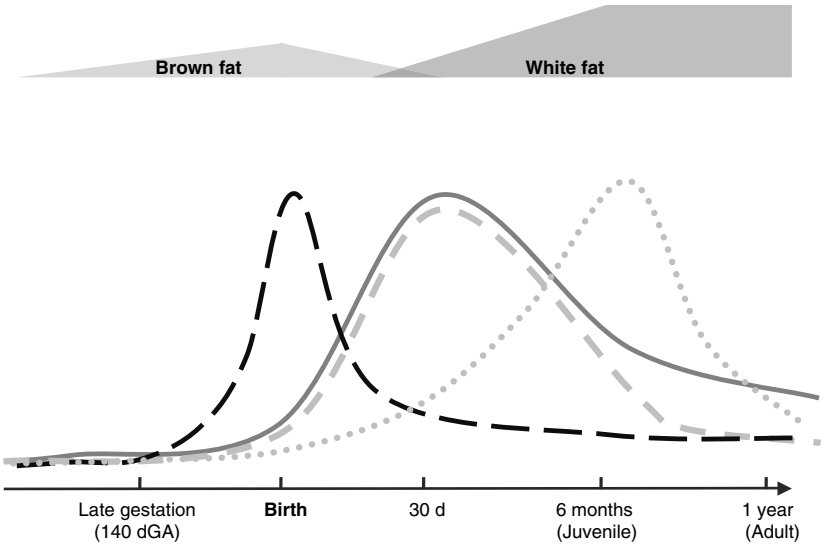

Fig. 2. Summary of the main changes in the characteristics of white adipose tissue during postnatal life. ––, Glucose-regulated protein 78 (GRP 78) mRNA; ——, toll-like receptor 4 (TLR4) mRNA; – – –, CD68 mRNA; ·····, IL-18 mRNA; dGA, d of gestation.

toll-like receptor 4 (TLR4) appears to have a critical role[42]. TLR4 is a major component of the innate immune system and is activated by its main ligand lipopolysaccharide. In addition, NEFA, plasma concentrations of which are normally raised with obesity[43], form a natural ligand for TLR4, inducing a local paracrine loop between macrophages and adipocytes[42,44].

It has recently been shown that gene expression for both TLR4 and the macrophage marker CD68 follow a similar developmental pattern in the sheep. Their abundance peaks at 30 d of age, coincident with the transition of brown to white adipose tissue and accompanying lipid accumulation[16], before declining to low concentrations in the adult[18]. The strong correlation between TLR4, CD68 and relative fat mass[19] may be indicative of elevated NEFA delivery to the adipose tissue as its abundance increases. This process would be predicted to promote TLR4 action, thereby enhancing the differentiation of preadipocytes and their subsequent pro-inflammatory properties[45]. In light of the close relationship between fat mass after birth and markers of both glucocorticoid action and inflammation, it has been possible to establish how these interactions may be reset, both after birth and in adolescence and early adulthood[19,37]. Importantly, that such adaptations can occur in the absence of any change in absolute fat mass implies that the latter is not required for all adverse metabolic outcomes[4].

The timing of maternal nutrient restriction and longer-term outcomes for adipose inflammatory and endocrine responses

Maternal nutrient restriction targeted to the period of very early adipocyte appearance in the fetus increases fat mass at term in conjunction with raised glucocorticoid action[37]. This response is accompanied by raised gene expression for UCP2, a characteristic of patients with visceral obesity[46], but occurs in the absence of similar effects on inflammatory markers[19]. However, even when the offspring are raised under an obesogenic environment they do not show increased fat mass compared with controls[4], although glucocorticoid action remains raised, at least in lean animals[37]. The same animals also show reduced gene expression of IL-18, an important mediator of the innate immune system[47]. Although, paradoxically, IL-18-knockout mice develop obesity and insulin resistance[48], plasma IL-18 concentration is actually raised in obesity[49]. Decreased IL-18 gene expression in the adolescent offspring born to nutrient-restricted mothers[19] could ultimately reduce appetite suppression and so increase food intake, promoting positive energy balance and consequent obesity. An adaptation of this type would be in accord with epidemiological studies of human populations exposed to early gestational nutrient restriction that demonstrate an increased risk of obesity in the offspring[50].

At birth, offspring exposed to mothers who have been nutrient restricted in late gestation have a reduced fat mass[51]. They do, however, show catch-up growth during the early postnatal period and thus restore their fat content to the same amount as offspring born to normally-fed mothers by 1 month of age. By 1 year of age they have an increased fat mass and are more likely to become glucose intolerant[52], which is similar to the epidemiological findings from historical cohorts[50]. A discrepancy between reduced fetal fat mass and increased juvenile adiposity in these offspring exposed to late gestational nutrient restriction suggests that a switch in fat growth during the early postnatal period is an important window in which later fat mass is set[21]. Over this period there is a marked increase in TLR4 gene expression in the adipose tissue of offspring born to nutrient-restricted mothers that is not evident in controls[19], in conjunction with a decrease in the abundance of CD68 on day 1 of life, a pattern that is subsequently reversed. This

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type of adaptation could determine later fat mass if white adipocyte precursors are committed during prenatal or early postnatal life[21].

At the same time, preadipocytes can be inhibited by macrophage-secreted factors, therefore suppressing conversion into mature adipocytes[53]. A lower macrophage content soon after birth is predicted to have important implications for early adipogenesis as adipose tissue undergoes substantial remodelling[54]. This stage of development therefore represents a highly-sensitive period during which the prenatal-programmed reduction in macrophage content, and hence macrophage-secreted factors, may allow more preadipocytes to mature. Ultimately, this process would enhance the adipocyte pool and could contribute to a greater fat mass in later life. Subsequently, with increasing adiposity, the marked rise in TLR4 could trigger pro-inflammatory mechanisms, in particular the NF-κB and c-Jun NH_2-terminal kinase pathways[42,55], further increasing the macrophage content[4]. This response in turn would be predicted to result in adipocyte and macrophage cross talk leading to a down-regulation of glucose–insulin signalling pathways, particularly of the glucose transporter, GLUT4[56], as seen at 1 year of age[52]. To date, such adaptations have only been described in offspring reared under free-living conditions. Clearly, future investigations need to examine the extent to which exposure to an obesogenic environment may accelerate or amplify these outcomes.

Conclusion

In conclusion, the early nutritional environment has a substantial impact on adipose tissue development, not only on the function of adipose tissue in the newborn but also on how it develops in later life. A better understanding of the primary factors and mechanisms that regulate the very different types of adipose tissue present in the fetal, newborn, postnatal, juvenile and adolescent periods has the potential to provide new therapeutic targets necessary to combat early obesity. The extent to which these processes differ between species must be seriously considered in the translational relevance in this area of research.

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